THE UNIVERSITY *of* EDINBURGH

AN INVESTIGATION OF THE MOBILITY OF PERI- AND ORTHO- SUBSTITUENTS IN ORGANIC COMPOUNDS.

by

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Generally speaking, the great achieve their greatness by industry rather than by mere brilliance. *Bruce Barton.*

Contents.

I. THE REACTION BETWEEN THIONYL CHLORIDE AND 8-NITRO-1-NAPTHOIC ACID, WITH AN ACCOUNT OF THE METHODS OF PREPARATION OF THE 8-HALOGENATED-1-NAPTHOIC ACIDS.

(a) Introduction.

The replacement of the nitro group in organic compounds was first observed by Kekulé (Ann. 1866, 137, 169) who found that by the direct treatment of nitrobenzene with bromine, he obtained tri-tetra and ponta- bromobenzenes. Twenty years later, Armstrong (J. Soc. Dyers, 1885, I, 85) observed the formation of bromo-dinitro phenol, on heating picric acid with bromine.

De Bruyn and Leent (Rec. Trav. Chim. 1896, 15, 84) studied the action of a saturated solution of hydrochloric acid on aromatic nitro- derivatives. The reactions were carried out in sealed tubes heated at temperatures ranging between 240°-270°, for periods of/

of from one to three hours.

By this method 1:3:5-trinitrobenzene was converted into 1:3:5-trichlorobenzene. Similarly the o- m- and p-dinitrobenzenes were converted into the corresponding chloro derivatives.

When 2:4:6-trinitrobenzoic acid was treated in an analogous way, the carboxyl group was first split off, and this was followed by the replacement of the nitro groups with chlorine.

A solitary experiment in the naphthalene series led to similar results. Treatment of 1:2:5:8-tetra-nitro-naphthalene in the above manner led to the formation of 1:2:5:8-tetrachloro naphthalene.

Atterberg/

Atterberg (Ber. 1876, 9, 316, 926, 1734) found that by passing chlorine into molten nitro compounds, a replacement of the nitro croup by chlorine took place. For example, α-nitro naphthalene is converted into α-chloro naphthalene by passing chlorine gas into the molten nitro compound.

It was observed by Jolin (Bull. Soc. Chim. 1877, II, 28, 514) that when dinitronaphthalene was heated with phosphorus pentachloride, the corresponding dichloro derivative was obtained. Incidentally he noted the ease with which naphthalene brominates, and moreover, that by merely shaking α-bromo naphthalene with nitric acid a mono nitro α-bromo naphthalene is obtained.

Schmidt and Ladner (Ber., 1904, 37, 4403) prepared halogen derivatives both in the benzene and phenanthrene series by heating mono-halogen mono-nitro derivatives with the appropriate ammonium salt. The reactions went forward in sealed tubes at a temperature of about 320°. Thus when o-bromo nitro benzene/

benzene was heated under those conditions with saturated ammonium chloride solution, o-dichlorobenzene was formed.

It was not, however, till 1915 that Meyer (Monatsch., 36, 723) studied the replacement of the nitro group by chlorine, using as effective reagent thionyl chloride at temperatures of 140°-160°.

When 4-chloro-3-nitro-benzene sulphonic acid was heated with thionyl chloride in a sealed tube at 140°, 1:3:4-trichloro-benzene was formed, both the nitro and sulphonic groups being replaced.

Almost quantitative yield of chlorobenzene and p-dichlorobenzene were obtained from nitrobenzene and p-chloro-nitrobenzene respectively.

On/

On the other hand, when m-nitrobenzene-sulphonic acid was similarly treated, only poor yields of m-dichlorobenzene were obtained.

Meyer also observed the easy halogenation of naphthalene. Thus by heating naphthalene with thionyl chloride at 170°-180°, 1:4 dichloronaphthalene was obtained.

A similar displacement was observed under very mild experimental conditions by Rule and Spence (J. 1929, 2516) in an attempt to obtain menthyl-8:nitro-1-naphthoate. The above workers warmed 8:nitro-1-naphthoic acid with thionyl chloride in the presence of benzene as solvent. Under these mild conditions the acid chloride of the 8:nitro acid was expected. The benzene and excess thionyl chloride were then removed by heating under reduced pressure and the acid chloride mixture treated with menthol. On working up the product in the usual way, an ester was obtained which contained no nitrogen, but gave a positive chlorine reaction. Analysis revealed the fact that the compound was menthyl-8-chloro-1-naphthoate. The presence of the chlorine atom in the 8 position was subsequently proved by hydrolysing the/

the ester to give 8-chloro-1-naphthoic acid.

The ester was isolated in a 25 per cent. yield.

The present work was undertaken in order to isolate the 8:chloro-1-naphthoic acid, without proceeding through the esterification stage, and the method is described in the following experimental section. 8:Bromo-1-naphthoic acid was prepared in a similar way using thionyl bromide. At first prepared merely out of curiosity, this acid was found to possess a definite theoretical and practical interest. Its easy preparation being a matter of necessity, recourse was had to the relatively efficient mercuration method described below.

(b) /

(b) Experimental.

The starting material in the preparation of 8-nitro-1-naphthoid acid was the α-naphthalene sulphonate of sodium, which, on distillation with potassium ferrocyanide, yields α-naphthonitrile. This on hydrolysis is converted to α-naphthoic acid, which by nitration is transformed in part into 8-nitro-1-naphthoic acid.

I. Preparation of α-naphthonitrile.

Dry sodium naphthalene α-sulphonate and dry potassium ferrocyanide are mixed in the proportions of 7:5. It is essential that the reactants be perfectly dry, and the carefully powdered sulphonate and ferrocyanide are first heated separately at 120° for 24 hours to achieve this result.

The mixture, (stirred with copper filings) is distilled in a bronze retort heated by means of a powerful ring burner. The purpose of adding the copper/

copper filings, is to distribute the heat quickly and uniformly throughout the mass. Sodium silicate is used to seal up the flanges of the retort. An air condenser is attached to the retort and the distillate is collected in a Buchner flask fitted to the end of the condenser. By applying a gentle suction, the reaction may be carried out under slightly reduced pressure.

The nitrile starts to distil over almost immediately. When no more liquid comes over, the product is taken up with ether, washed with dilute sodium hydroxide, dilute hydrochloric acid, and finally with water. The fluorescent ether extract is dried over calcium chloride.

On removal of the ether, the nitrile is distilled in vacuo. The fraction boiling between 160°-165° under 18 mm. was collected. A small amount of naphthalene passes over in the initial reaction (due, probably, to a certain amount of local over heating), but as this is removed in the next stage, further purification of the nitrile was not attempted.

Yield (from 400 grams of sulphonate-ferrocyanide mixture), 50 grams.

Whitmore and Fox (J.A.C.S., 1929, 51,3367) record/

record that no yield of α-naphthonitrile was obtained by the Sandmeyer reaction. Other workers, however, Clarke and Read (J.A.C.S., 1924, 46, 1001) and J. McRae (J.A.C.S., 1930, 52, 4550) have shown that the nitrile is obtainable by this reaction. It appeared of interest therefore to carry out the Sandmeyer reaction on α-naphthylamine and for this purpose the procedure used was similar to that indicated in Organic Syntheses (Clarke and Read, vol. IV, p. 69) for the preparation of o-tolunitrile. The yield of the nitrile was small, however, and in the general preparative work, the first method was used.

II. Preparation of α-naphthonitrile from α-naphthylamine.

This method consists essentially in the addition of a solution containing diazotised α-naphthylamine to a solution of cuprous cyanide at a low temperature (0°).

Preparation/

Preparation of the cuprous cyanide solution.

312 grams of copper sulphate crystals were mixed with 81 grams of sodium chloride and dissolved in three litres of hot water contained in a four litre beaker. To this was added during the space of ten minutes a solution of 66 grams of sodium bisulphite and 44 grams of sodium hydroxide in 500 c.c. of water. The white precipitate and supernatant liquid were allowed to cool to room temperature and the liquid poured off. The white precipitate was washed by decantation several times with cold water containing a little sulphur dioxide. The white solid was now suspended in 250 c.c. of cold water in a three litre jar, and 162 grams of sodium cyanide in 750 c.c. of water were added with stirring, the whole being kept cool by surrounding with ice water.

Preparation of the diazo salt.

143 Grams of α-naphthylamine (A.R.) were mixed with 200 c.c. of 28 per cent. hydrochloric acid, and poured into a five litre jar. The jar was surrounded by ice and kept at 0°C. 70 Grams of/

of sodium nitrite in 200 c.c. of water were continuously added with stirring. The resultant product was neutralized cautiously with 50 grams of sodium carbonate, and the mixture carefully stirred. At this stage it was neutral to litmus.

The cuprous cyanide solution was now cooled to 0° by the addition of ice, and one litre of benzene was poured on its surface. To this was slowly added the cold neutral diazonium salt solution. During the addition which occupies about thirty minutes, such vigorous stirring is maintained that the benzene on the surface is constantly drawn to the stirrer, and the temperature is kept at 0°-5° by the addition of ice. As soon as the diazo solution comes into contact with the cuprous cyanide, a brown precipitate appears which is taken up in the benzene as soon as it is formed. Nitrogen is evolved continuously during the process. When all has been added the temperature is kept at 0°-5° for thirty minutes and then allowed to rise to room temperature. The line of demarcation between the benzene and aqueous layers was not very clear, so the product was subjected to steam distillation, and from the benzene which came over, a little tarry liquid was obtained/

obtained by evaporation. The effect of the steam however had been to break up the emulsion, and the distillation was stopped. The contents of the flask were cooled, the brown oily liquid was taken up with chloroform, and the chloroform layer dried. The chloroform was removed, and the residue fractionated in vacuo. The portion boiling at 145°-149° under 10 mm. was collected. A 20 per cent. yield of α-naphthonitrile was obtained by this reaction.

Hydrolysis of α-naphthonitrile.

Kamms (private communication to Whitmore and Fox, J.A.C.S., 1929, 51, 3383) records the hydrolysis of α-naphtho-nitrile with a mixture of sulphuric and acetic acids and water. The product so obtained is, however, highly impure (Whitmore and Fox, loc. cit).

The method of hydrolysis used by us was as follows: 100 grams of potassium hydroxide were dissolved in 100 c.c. of water; 500 c.c. of alcohol were/

were added, followed by 120 grams of α-naphthonitrile. The mixture was heated in an autoclave on an air bath. The inside temperature of the mixture was kept at 140°-160° for three hours during which time the pressure rises to 60-80 pounds/square inch, while a continuous current of ammonia is given off at the side valve.

After cooling, the autoclave was opened with the usual precautions and the alkaline yellow liquid so obtained was boiled to remove alcohol. After dilution with water, and filtration from naphthalene, the naphthoic acid was precipitated with dilute sulphuric acid. So obtained, the naphthoic acid does not require further purification.
Yield - 126 grams (93% of theory).
Melting point 159°-160°.

Gilman, St John and Schulze (Org. Syn., vol. XI, 80) claim a 68-70% yield of α-naphthoic acid obtained by performing the Grignard reaction on α-bromo naphthalene.

Preparation/

Preparation of 8-nitro-1-naphthoic acid.

The main products of the nitration of 1-naphthoic acid are 5.nitro-1-naphthoic acid and 8-nitro-1-naphthoic acid. In previous work it was found that the amount of 5-nitro acid formed was greatly in excess of the amount of 8-nitro acid. The yield of 8-nitro-1- naphthoic acid was, however, found to be improved by keeping a low temperature of nitration.

120 Grams of 1-naphthoic acid were mixed with enough concentrated nitric acid (450 c.c.) to form a smooth paste. This was placed in a round bolt-head flask (2 litre) fitted with a mechanical stirrer. A vigorous reaction took place and the flask was cooled with water. After the initial reaction was over, the mixture was warmed to 60° with stirring, and kept at this temperature for two hours. It was then allowed to cool, being continuously stirred during the course of 3-4 hours. The nitrated product was then poured into two litres of water, and allowed to stand, with occasional stirring, for an hour. After filtration and washing, the acids were dissolved in sodium carbonate solution, and the product filtered. This was done in order to remove/

remove any nitro naphthalene which might have been formed. Actually under the conditions of nitration, none of this substance was formed.
Yield of mixed acids - 150 grams.

Separation of the 5- and 8-nitro-1-naphthoic acids by fractional crystallisation from alcohol.

Advantage is taken of the relative insolubility of the 5-nitro acid in alcohol (Eckstrand). One part of the 5-nitro acid dissolves in 187 parts of absolute alcohol, while one part of the 8-nitro acid is soluble in 21.5 parts of absolute alcohol at room temperature.

The mixed acids (150 grams) were dissolved in 1312 c.c. of absolute alcohol, and the solution filtered from a certain amount of insoluble residue. (Possibly 5:8-dinitro-α-naphthoic acid). The filtrate on cooling, deposited a first crop of crystals which were filtered off in the cold (50 grams). These were dried in the steam oven. On standing for another 16 hours at 0°C., another crop of crystals were obtained, filtered, and dried (10 grams).

After a further 16 hours only a small quantity/

quantity of solid was deposited.

The filtrate was evaporated to dryness, and crude 8-nitro-1-naphthoic acid remained (76 grams).

Purification of 8-nitro-1-naphthoic acid by esterification of the 5-nitro acid present as impurity.

The 5-nitro acid is easily esterified in the presence of absolute methyl alcohol and dry hydrogen chloride, while the 8-nitro acid can exist unchanged under these conditions for a long time (Eckstrand). The crude 8-nitro acid was dissolved in 500 c.c. of methyl alcohol, and a few drops of concentrated sulphuric acid added. The mixture was refluxed for 4 hours during which time a steady current of hydrochloric acid gas was passed into the solution.

The product was then poured on to a mixture of ice, and sodium carbonate was added in excess. Methyl 5-nitro-1- naphthoate remained undissolved. After filtration the filtrate was heated to remove some of the alcohol, and the 8-nitro-1-naphthoic acid liberated by acidification with concentrated sulphuric acid. The mixture was warmed on the steam bath for half an hour, cooled, and filtered. The solid product was washed with water till free from mineral/

mineral acid. The acid was then dried on a porous plate in the steam oven. When dry it was a white amorphous product melting at 214°-215°. It was judged pure enough to use in the following experiments.

Yield - 35 grams.

Using a higher temperature of nitration, the yield of 8-nitro-1-naphthoic acid fell to 24 grams starting from a similar quantity of mixed nitro acids.

Another method of separation of 5- and 8-nitro-1-naphthoic acids.

The following method was tried out but found to be less efficient than the above process of dissolving the mixed acids in absolute alcohol.

A mixture of 5- and 8-nitro acids was dissolved in the calculated amount of sodium hydroxide solution, and slightly more than the calculated amount of hydrochloric acid required to precipitate the quantity of 5-nitro acid expected in the mixture was added with vigorous stirring. The precipitated acid was filtered off, and the filtrate acidified. After standing for some hours, the separated 8-nitro acid/

acid was removed by filtration and dried. It melted at 192°-196°, and was purified by the fractional esterification method. This procedure was suggested by the fact that the 8-nitro acid would be expected to be a considerably stronger acid than the 5-isomeride.

In discussing the action of thionyl chloride on the nitro acid, separate consideration will be given to the three different sets of conditions under which the reaction was carried out.

1. The action of boiling thionyl chloride on 8-nitro-1-naphthoic acid in the absence of solvent.

10 Grams of the nitro acid were mixed with 50 grams of thionyl chloride in a round flask fitted with a ground-in air condenser. The product was refluxed on an oil bath for 10 hours. After cooling the flask and its contents in the refrigerator overnight, needle shaped crystals were found to have separated out. These were filtered off and the filtrate reserved.

The crystals were washed with benzene and the benzene washings discarded. After drying in the oven/

oven,the solid product was recrystallised from chloroform when it separated as yellow-green needles. These melted at 264°-266°C. After another recrystallization from boiling alcohol, they melted at a slightly higher temperature (269°-270°). Another recrystallization had no effect on the melting point. The yield of pure product was 3 grams.

An elements test revealed the presence of nitrogen and chlorine, which suggested the acid chloride of a nitro acid. The product was insoluble in water, and was boiled with alcoholic potassium hydroxide. After removal of some of the alcohol and dilution with water, the original product was recovered unchanged. The crystals were therefore not those of an acid chloride.

Eckstrand (J. Pr. Chem. [2] , 38, 174) records the formation of a compound, dichloronaphtho styril ,(melting point 264°-265°) which appeared to bear a resemblance to the above product. Some of this compound was therefore prepared by Eckstrand's method.

Preparation/

Preparation of dichloro naphthostyril.

15 Grams of 8-nitro-1-naphthoic acid were mixed with excess of fuming hydrochloric acid in a Carius tube which was then sealed off in the usual way. The tube and contents were heated in the furnace for two hours at 150°C. After slow cooling and immersion in a freezing mixture, the tube was opened, and the contents poured into water. The mixture was extracted with ether, and washed twice with sodium hydroxide to remove acidic products, and then with water until free from alkali. The ether extract was dried and the ether removed. The residual solid was transferred to a filter and washed with cold ether till free from any smell of naphthalene, and finally twice recrystallised from boiling alcohol.

A mixed melting point of the dichloro-naphthostyril so obtained, and the substance prepared by the thionyl chloride reaction, melted at 267°. The two are therefore assumed to be identical.

Eckstrand did not describe the orientation of the chlorine atoms in this compound, and this was not determined by us, as being unnecessary from the/

the point of view of the present work. We assume, however, that the position occupied by the chlorine atoms are the 5- and 7. If the formation of the compound is preceded by the reduction of the nitro-compound to the amino compound, as seems probable, the NH_2- group would normally direct to the positions 5- and 7-.

The substance is soluble in boiling chloroform and alcohol. It is less soluble in ether, giving a green fluorescent solution. It is soluble in sodium hydroxide (concentrated) at the boiling point.

2. The action of thionyl chloride on 8-nitro-1-naphthoic acid in the absence of solvent at room temperature.

1 Gram of the nitro acid and 6 grams of thionyl chloride were left in contact at room temperature for 36 hours. The product was diluted with benzene, shaken and filtered. The dried residue/

residue was recrystallised from chloroform and melted at 266°. Weight 0.25 gram.

3. The action of thionyl chloride on 8-nitro-1-naphthoic acid in benzene solution at the boiling point.

30 Grams of thionyl chloride were mixed with 150 c.c. of benzene, and added to 10 grams of the nitro acid contained in a round flask with ground-in air condenser. After warming the flask gently, the reaction started but gradually eased off. Finally however, after surrounding the flask with water at 50° the reaction started without further heating. After 24 hours the mixture was refluxed on an oil bath for half an hour, when a clear, red-brown solution was obtained. The benzene and excess thionyl chloride were removed at the pump, the flask being surrounded by an oil bath at a temperature of 110°C.

The syrupy product was now boiled repeatedly with small quantities of water. The hot aqueous extracts after filtration, deposited on cooling, small platelets which were filtered off and dried. Melting point 162°-166°. By repeated crystallisation from benzene, the final product melted at 167°-168°.

Weight/

Weight 2.5 grams.

Eckstrand (J. Pr. Chem. [2], 38, 267, 1885) gives 168° for 8-chloro-1-naphthoic acid.

As 8-nitro-1-naphthoic acid is soluble to some extent in water, and as none was isolated by repeated boiling of the residue with water, it was assumed that a certain amount of 8-nitro acid chloride, formed during the reaction, was stable towards boiling water. The residue in the flask was then treated with dilute sodium hydroxide and warmed, when most of it passed into solution. The mixture was filtered.

(a) Examination of the filtrate.

The filtrate was acidified and a brown tarry product separated, which was filtered and boiled with aqueous alcohol in the presence of animal charcoal. After filtration the filtrate deposited yellow crystals of melting point 210°. A mixed melting point with pure nitro-acid gave 211°.

Weight 3 grams.

(b) Examination of the alkali insoluble residue.

This residue was dissolved in boiling alcohol and on cooling deposited a brown solid, which on recrystallisation from chloroform melted at 262°.

A/

A mixed melting point with dichloro naphthostyril gave 264°-265°.

Yield 1.5 gram.

The chloroform residues on evaporation gave a tarry product which could not further be worked up.

Having investigated the general nature of the reaction between the nitro acid and thionyl chloride, attempts were made to improve the yield of the chloro acid. These attempts were unfortunately unsuccessful, but a resume follows of the results obtained.

(1). If instead of removing the benzene and excess thionyl chloride at the pump, the product is poured on to ice, and the benzene removed on the steam bath, a slightly different result is obtained. The 8-chloro acid can be extracted by boiling the residue with water, but a poorer yield of less pure product is obtained.

(2). If after boiling the thionyl chloride with the nitro acid in the absence of solvent, and taking off the excess thionyl chloride at the pump in the cold, the residue be boiled with water, only a poor yield of chloro acid is obtained.

(3) /

(3). Schmidt and Ladner (Ber. 1904, 37, 4403) show that by heating o-brom nitrobenzene at 320° in a sealed tube with ammonium chloride, the following reaction occurs.

When however, a small quantity of the nitro acid was heated with saturated calcium chloride solution at 260°, almost complete carbonisation took place.

(4). It was thought that the use of sulphuryl chloride instead of thionyl chloride would give rise to a better yield of chloro acid, since in this case the absence of reducing properties in the reagent should avoid the formation of dichloro-naphthostyril. When, however, the nitro acid was boiled with excess of sulphuryl chloride for 24 hours, no apparent reaction took place, the acid not dissolving in the reagent. The experiment was then carried out in benzene solution.

The action of sulphuryl chloride on 8-nitro-1-naphthoic acid in benzene solution.

30 Grams of sulphuryl chloride were mixed with 3 grams of 8-nitro-1-naphthoic acid and heated for 18 hours, after which time the acid had gone completely into solution. On cooling it was observed that a large amount of blackening had taken place.

The/

The excess sulphuryl chloride and solvent were removed under reduced pressure in the usual way, and the mixture repeatedly extracted with boiling water. The extracts were filtered and cooled . The separated crystals were filtered off, dried, and recrystallized from ligroin.
Melting point 168°-169°.
The weight 0.2 gram, represents a 7% yield of chloro acid.

The water-insoluble residue was completely soluble in sodium hydroxide solution, except for a small amount of carbonaceous matter which was filtered off. This complete solubility indicated the absence of dichloronaphthostyril. By the addition of hydrochloric acid to the extract, and purification of the precipitate, 1.5 grams of nitro acid were recovered.

From the above experiments we arrive at three main conclusions.

(a), Thionyl chloride acts as a reducing agent in this reaction, whereas sulphuryl chloride is incapable of acting in this capacity.

(b). Thionyl chloride can act as a chlorinating agent. It is well known that a substance containing

a/

a nitro-group undergoing reduction is easily chlorinated (Blanksma, Proc. K. Adad. Wetensch. Amsterdam, 1906, 8, 680).

(c). That sulphuryl chloride may be used to replace a nitro-group with a chlorine atom in an organic compound, but under the experimental conditions used, is not as effective for this purpose as is thionyl chloride.

When treated with thionyl chloride in benzene solution in the above manner, 5-nitro-1-naphthoic acid yields no detectable trace of 5-chloro-1-naphthoic acid, but is recovered unchanged. As o-nitro-1-benzoic acid bears a structural resemblance to 8-nitro-1-naphthoic acid, it appeared of interest to study the action of thionyl chloride on this acid.

Under precisely similar conditions to the aforementioned, some o-nitro benzoic acid was dissolved in benzene in the presence of thionyl chloride and the product left overnight after the initial reaction had subsided. The benzene and excess thionyl chloride were removed under diminished pressure, and the residue treated with methyl alcohol. After an hour's heating, no more hydrochloric/

hydrochloric acid gas was evolved, and the excess methyl alcohol was removed on the steam bath. The ester was taken up with ether and washed. On distillation, only methyl o-nitro benzoate was isolated, no trace of the o-chloro ester being detected. The possibility of the replacement of the nitro group in this compound by thionyl chloride wa under more vigorous conditions was not investigated.

Having obtained 8-chloro-1-naphthoic acid by the action of thionyl chloride on 8-nitro-1-naphthoic acid, it was decided to test the action of thionyl bromide on the nitro acid. For this purpose thionyl bromide was prepared as described below.

Preparation of thionyl bromide.

When hydrobromic acid gas is passed into boiling thionyl chloride, a certain amount of reaction takes place to form thionyl bromide. The yield is small however, and the product is contaminated with bromine. On the other hand, if the experiment be carried out at room temperature, very little reaction takes place. In the following experiment an intermediate temperature was therefore adopted, namely, about 60°C. In essentials the method/

method employed by us was similar to that of A. Besson (Compt. rend. 1896, 320). Hydrobromic acid gas was prepared by the action of dry bromine on benzene, in the presence of an aluminium-mercury couple. The hydrobromic acid was passed through one neck of a three-necked Woulf's bottle, fitted with condenser and thermometer, into thionyl chloride. The bottle was surrounded by water kept at 60°-70°C. Excess hydrobromic acid gas, above that calculated for complete conversion, was prepared and passed through the thionyl chloride. The heavy, fuming, dark red liquid was then fractionated, and the product distilling at 78°-80° under 86 mm. was collected (Besson records about 68°/40 mm.). The yield under these conditions was nearly quantitative.

It may be mentioned at this point that attempted preparations of thionyl iodide were unsuccessful. Passing the hydriodic acid gas into thionyl chloride even at a low temperature was found to lead to the production of sulphur, and no thionyl iodide could be isolated.

When potassium iodide and thionyl chloride are heated together, interaction takes place, but the product decomposes on distillation.

Preparation/

Preparation of 8-bromo-1-naphthoic acid.

10 Grams of 8-nitro-1-naphthoic acid were mixed with 30 grams of thionyl bromide in 150 c.c. of benzene. The product was heated till solution took place, and allowed to stand for 12 hours. The benzene and excess thionyl bromide were removed at the pump, and the residue extracted with small quantities of hot water. The aqueous extracts were filtered and cooled. Small crystals were deposited, which were filtered, washed, and dried. Two recrystallisations from benzene gave a product melting at 178°C. The substance was a free acid; it contained no nitrogen, but bromine was found to be present.

The weight of pure product was 1.5 grams, representing a 9% yield.

Analysis: Calculated Br 31.87%. Found Br 32.12%.

Preparation of 8-bromo-1-naphthamide.

1 Gram of the bromo acid was dissolved in 3 grams of thionyl chloride ina small flask fitted with a ground-in air condenser. After half an hour no further evolution of gas could be detected. The excess thionyl chloride was removed under diminished pressure/

pressure and excess ammonium carbonate was added and ground up with the acid chloride by means of a stirring rod. Evolution of gas (CO_2) occurred. The product was transferred to a filter, using hot water, and washed several times. On recrystallisation from benzene, crystals of melting point 179°-180° were obtained, which were insoluble in sodium carbonate solution. A mixture of these and the bromo acid melted over a range of temperatures beginning at 135°C.

Analysis: Calculated. Br 32.0%. Found. Br 32.18%.

Preparation of methyl ester of 8-bromo-1-naphthoic acid.

One gram of the bromo acid was dissolved in 3 grams of thionyl chloride at the ordinary temperature and the excess thionyl chloride removed under reduced pressure. When the reaction was completed, 3 c.c. of methyl alcohol were added, and the product heated until no further evolution of hydrochloric acid gas took place. The mixture was then poured into water, and the ester taken up with ether. The ether extract was washed with dilute sodium hydroxide solution/

solution, then with hydrochloric acid, and finally with water till free from acid. After drying over calcium chloride the ether was distilled off, and the ester obtained as an oil. This was left in a vacuum desiccator for four days, after which time it had solidified. Several recrystallisations from petrol ether gave a maximum melting point of 33°C.

Analysis: Calculated. Br, 30.2%. Found. Br, 30.4%.

A preparation of the 8-bromo-1-naphthoic acid was also tried by direct treatment of α-naphthoic acid with bromine.

Attempted preparation of 8-bromo-1-naphthoic acid by bromination of α-naphthoic acid.

3 Grams of α-naphthoic acid were dissolved in glacial acetic acid, and introduced into the lower end of a Carius tube by means of a long funnel. 4 Grams of bromine, (slightly less than the calculated amount) were added to the above solution. The tube was sealed off in the usual way, and heated in the furnace for 8 hours at 140°C. After cooling, all the bromine coloration had disappeared. The tube was opened, and dense white fumes of hydrobromic acid gas/

gas were given off. The product was filtered and the acetic acid filtrate separated from the crystals present. The crystals were washed with a little glacial acetic acid, and this washing added to the above filtrate. The crystals were then washed with water and recrystallised from boiling rectified spirit. They melted at 242°-243°C. and consisted of 5-bromo-1-naphthoic acid. Yield 3 grams. Hausamann quotes 240°C. as the melting point of this acid.

The acetic acid filtrate was diluted with water and the precipitate filtered. This, on recrystallisation from water, melted at 158°C. A mixed melting point with naphthoic acid gave 159°-160°C. Weight 0.5 gram. No 8-bromo-1-naphthoic acid could be isolated from this reaction.

As the peri-bromo acid was required for future experiments an easier method for its preparation was sought in the work of Lenck, Perkins and Whitmore (J.A.C.S. 1929, 51, 1831).

Their method consists in the mercuration of naphthalic acid, and the subsequent decomposition of the resulting product by treatment with bromine.

This method is of considerable practical importance for the preparation of the 8-halogenated compounds.

The mercuration of naphthalic acid. (Lenck, Perkins and Whitmore, loc. cit.).

50.5 Grams of naphthalic acid are dissolved in a mixture of 1200 c.c. of water and 31 grams of sodium hydroxide. This is added to a solution of 55 grams of yellow mercuric oxide in 150 c.c. of water and 40 c.c. of glacial acetic acid. An excess of acetic acid is added, and the mixture is refluxed for 96 hours on an oil bath at 140°C. Carbon dioxide is evolved in large quantities during the first twelve hours, but the amount given off gradually lessens till at the end of the above period, no gas is given off as tested for with lime water. Moreover a sample of the solution deposited no metallic mercury on a clean copper wire. The precipitate was filtered off, washed with glacial acetic acid, water, alcohol, and finally ether. It was dried for several hours at 140°C.
Weight 85 grams.

The/

The formation of 8-bromo—1-naphthoic acid from the above mercuration product.

The above authors give no directions for the preparation of this acid although they state that they can obtain it in good yield. The method used by us was as follows:- 20 grams of mercuration product were dissolved in 20 c.c. of 5 N. sodium hydroxide solution and 100 c.c. of water. The solution was boiled with animal charcoal and filtered. The filtrate was barely acidified with hydrochloric acid, and the chloro mercuri derivative then separated by filtration. Without further treatment it was suspended in 250 c.c. of glacial acetic acid, and treated with 9 grams of bromine in a concentrated solution of sodium bromide. The chloro-mercuri-derivative dissolved almost immediately, and the mixture was just brought to the boil. After standing for half an hour, the product was poured into a large volume of water, well shaken, and the crystals filtered These weighed 7 grams.

The purification of the bromo acid proved to be a very tedious matter. Water was found to be the best solvent, and after several recrystallisations, a yield of 2.5 grams of relatively pure bromo acid

was/

was obtained. Melting point 176°-177°C.

A similar method of preparation was adopted for the preparation of the chloro acid.

Preparation of 8-chloro-1-naohthoic acid from mercurated naphthalic acid.

20 Grams of the mercuration product were treated exactly as in the previous experiment. To the suspension of the chloro-mercuri-compound in acetic acid were added 4 grams of chlorine dissolved in 50 c.c. of glacial acetic acid. After bringing to the boiling point the solution was poured into 500 c.c. of water, and the product cooled in ice for several hours. The brown precipitate which formed was filtered and recrystallised from water as before. Melting point 168°-169°C. Weight 3 grams.

Various unsuccessful attempts to prepare 8-iodo-1-naphthoic acid may be briefly summarised thus:-

(1) The attempted preparations of thionyl iodide were unsuccessful and thus this approach to the iodo acid via the nitro acid was closed.

(2) /

(2) When the mercuration product was treated as for the bromo acid, except that iodine in potassium iodide was used in place of bromine, naphthoic acid (melting point 160°C) was formed together with mercuric iodide, but no iodo-naphthoic acid could be obtained.

(3) Treatment of the mercuration product with iodine chloride led to results similar to those obtained in (2).

(4) The chloro-mercuri-compound was suspended in water in a flask under reflux. A concentrated solution of iodine in potassium iodide was then slowly added as long as decolorisation took place. The mixture was then boiled for another hour, filtered and washed. The filtrate was then made strongly acid with hydrochloric acid, and filtered. The crystals so obtained melted at 155°C., and by repeated crystallisation from dilute acetic acid, benzene, and ligroin, the melting point was raised to 165°-167°C., but no further. This possible contained a small amount of iodo acid, but the melting point is unexpectedly low. An iodine analysis was carried out on this product but the iodine content was nearly twice the calculated amount for 8-iodo-1-naphthoic acid.

(5) /

(5) Attempts to prepare the iodo acid by reduction of the 8-nitro-1-naphthoic acid with ferrous sulphate, followed by diazotisation of the amino acid and treatment with potassium iodide, were unsuccessful.

The method of analysis of the bromo compounds in this thesis was that of Elvira? and Thomson (J.A.C.S., 1930, 52, 1893). Accurate results were obtained and the method is to be recommended because of the small quantities of bromo compound required in the analysis.

II. THE REACTIVITY OF THE HALOGEN ATOM IN O-IODO BENZOIC ACID UNDER THE INFLUENCE OF A CATALYST (NATURKUPFER C) AND SOME USES OF THIS COMPOUND AS A SYNTHETIC AGENT.

(a) Introduction.

It has been known to chemists for many years that a halogen atom attached to the benzene nucleus is capable of being activated by other groups present in the ring.

Probably the earliest observation of this effect was made by Pisani (Ann. 1854, 92, 326) who studied the activation of the halogen atom in picryl chloride. The point of interest about this substance is that it behaves like an acid chloride, reacting with ammonia and yielding picramide.

Schöpff in 1891 summarised the state of knowledge in the subject, when he stated that if in a benzene nucleus containing a halogen, there were also present two m-directive groups such as $-NO_2$, $-SO_3H$, -COOH, -CN, or $-COOCH_3$, then an activation of the halogen atom took place. The groups (which did not need to be similar) exerted their effects if in the o- or p- position to the halogen atom. If only one negative group were present, no activation took place unless that were the nitro group.

For example, when 2-bromo-3-nitro-benzoic acid is heated with aniline, condensation takes place according to the equation.

Similarly when aniline was heated with o-nitro-chloro-benzene, mono-nitro-diphenylamine was formed.

In the same way using benzidine instead of aniline, the reaction expressed in the following equation took place.

Although/

Although in general, only m-directive groups render o-substituents reactive, Taubenheimer (Ber. 1876, 9, 1826), and Tiemann (Ber. 1891, 24, 709) have shown that, on occasion, o- and p-directive substituents may increase the mobility of substituents in the m-position. For example, although o-dinitro-benzene is only converted into o-nitraniline after heating with alcoholic ammonia for ten weeks, the similar reaction with 5-chloro-o-nitro benzene is completed in five days.

In an analogous manner 4-nitro-2-chloro-benzaldehyde is converted into o-chloro p-anisaldehyde by treatment with sodium methoxide; p-nitro-benzaldehyde is stable towards this reagent.

The work of Ullman and Bruck (Ber. 1908, 41, 3932) bore out the conclusion of Schöpff, in the field of polynitro-naphthalenes. Thus when benzylamine and 1-chloro/

1-chloro-2:4-dinitro-naphthalene interacted, 1-benzyl-amino-2:4-dinitro-naphthalene was formed.

Borsche (Ber. 1909, 42, 601) used this activating effect as a synthetic means in the preparation of derivatives of sodium acetoacetate. By the interaction, for example, of 2:4-dinitro-chlorobenzene, and sodium acetoacetate, a 75% yield of ethyl α-2:4-dinitro-phenyl acetoacetate can be obtained.

Kenner and co-workers (1914-1927) have studied the activating effect of the group in halogenated nucleii. They have further shown that the activating effect may take place through a series of atoms which do not all form part of the aromatic nucleus.

Even more recently Clarke and Hall (Trans. Roy. Soc. Canada, 1927, iii, 21, III, 311-314) have demonstrated the replacement of -Cl by -OMe using nitro-halogen-compounds in the presence of concentrated sodium methoxide solution in a sealed tube at/

at a high temperature.

Ingold's theory (which in this case is merely the modern restatement of the conclusions of Lapworth, Robinson and, to a smaller extent Flürscheim) explains how a group such as the $-CH_3$ which repels electrons, will have a deactivating influence on nuclear hydrogen. The $-NO_2$ or -COOH group, on the other hand, which attract electrons, will activate strongly the o- and p- positions. Not only is the effect of the nitro group transmitted through the bonds, but a direct space effect will also be evident. This space effect will also diminish with the distance from the activating groups in the order o->m->p-. Although therefore, in a nitro derivative this spatial influence will activate the m- position to a greater extent than the more distant p- position, this effect is small in comparison with the electronic effect transmitted to the o- and p- positions. Thus the o- and p-chloro-nitro benzenes are much more readily hydrolysed than m-chloro-nitro-benzene.

Further we may say that the o-chloro compound is in general more reactive than the corresponding p-derivative, because of the greater space effect of the nitro group on this position.

The/

The relatively recent work of Wood and Davies (J. 1928, 1122) has testified to the enormous effect of the $-NO_2$ group as compared with the other m-directive groups such as -COOH, $-SO_3H$ etc. They have studied the high reactivity of 1:3-dichloro-4:6-dinitro-benzene as compared with the almost inactive 1:3-dichloro-4:6-benzene disulphonic acid. In compounds of the type, , where x can be either $-NO_2$, $-SO_3H$ or -COOH, the chlorine atom is concluded to be 70,000 times more active when x is the nitro group, than when the substituents are $-SO_3H$ groups. Moreover the nitro groups activate the -Cl atom 200,000 times more strongly than do carboxyl groups in similar positions.

These facts lend additional interest to the observations of Rosenmund and Harms (Ber. 1920, 53, 2231) who showed that the halogen atom in o-bromo benzoic acid in presence of Naturkupfer C catalyst is much more reactive than formerly realised. Hurtley (J.C.S., 1929, 1870) extended the observation of these two workers and made the reactivity of the halogen atom in o-bromo benzoic acid a means of preparation/

preparation of certain o-substituted benzoic acids. The conclusions of Hurtley may, with advantage, be summarised under three headings.

(a) Using dry copper acetate or preferably copper bronze catalyst (Naturkupfer C), the bromine atom in o-bromo-benzoic acid is activated to such an extent that its reaction with the sodium derivative of diethyl malonate, ethyl acetoacetate, ethyl acetone dicarboxylate, acetyl acetone, and benzoyl acetone in boiling alcohol is a matter of extreme ease. For example the sodium derivative of diethyl malonate gave

and with the sodium derivative of ethyl acetoacetate, mono ethyl homophthalate was the only product isolated.

(b) The ethyl ester of the bromo acid is non-reactive under the above conditions, as is also free p-bromo benzoic acid.

(c) /

(c) o-Bromo-nitro-benzene does not enter into the above reaction when treated similarly to the o-bromo acid.

From the theoretical point of view the conclusion arrived at in (c) is probably of the greatest interest. At the moment it is inexplicable, however, for from the previous observations this compound should be considerably more reactive than the bromo acid.

The reactivity of the o-bromo atom suggested a method, which is described in the following pages, for the preparation of certain o-ethers. Up to the present, the methods of preparing these compounds have been rather crude. Ullmann's method which consists in heating the sodium salt of an alcohol or phenol with a halogenated compound in the presence of copper powder at 160°-180°C. in a tube for several hours, is often unsuccessful, due, among other things, to the resultant decomposition. Unfortunately it was found that no reaction takes place on boiling a methyl alcoholic solution of sodium methoxide with the sodium salt of the bromo acid in the presence of copper bronze.

Experiments/

Experiments were therefore carried out using o-iodo benzoic acid with the results outlined below. It was noticed that although p-iodo benzoic acid could not be converted into the corresponding methoxy acid by the above treatment (owing, possibly, to the insolubility of its sodium salt in alcohol), it was readily converted to the corresponding hydroxy acid by boiling for an hour with bench sodium hydroxide in the presence of copper bronze catalyst.

It would appear therefore that the activating effect of the -COOH group extends to both the o- and p- positions under the circumstances. On the other hand it was observed that the p-bromo-nitro-benzene was not reactive under similar experimental conditions.

One of the most interesting points of difference between the iodo and bromo acids was the fact that whereas the ethyl ester of the bromo acid was inactive towards the reagents employed by Hurtley, the methyl ester of the iodo acid reacted with sodium methoxide to give methyl-o-methoxy benzoate.

The conversion of the o-bromo benzoic acid into the iodo acid by boiling the sodium salt of the former with sodium iodide in ethyl alcoholic solution, illustrates a variation of the method using sodium iodide in acetone solution, and demonstrates, moreover, the extraordinary reactivity of the bromine atom under consideration. Formerly this method of obtaining iodo compounds from chloro and bromo derivatives was confined to compounds containing a side chain halogen, or to aliphatic derivatives containing an active halogen atom.

(b) Experimental.

In the following experiments enough sodium was added to form the sodium salt of the iodo acid as well as to provide the required quantity of sodium alcoholate or phenoxide.

The catalyst used, was, in each case, (except where otherwise stated) finely divided copper bronze. The amount of catalyst added is not of importance, but was usually kept between the limits of 0.2-0.5 grams in each of the following examples.

Preparation/

Preparation of o-iodo benzoic acid (cf. Cohen and Raper, J.C.S., 1904, 85, 1272).

16 Grams of anthranilic acid were dissolved in dilute sulphuric acid (25 c.c. of concentrated in 125 c.c. of water), and the whole cooled in ice to 0°C. A solution of sodium nitrite (10 grams in 20 c.c. of water) was added, drop by drop with stirring, the temperature being kept down if necessary by the addition of ice. The addition of sodium nitrite was continued until excess was present, as tested for by starch iodide paper; 30 grams of potassium iodide (in 50 c.c. of water) were then added cautiously with stirring, and the product allowed to stand at room temperature overnight. It was then warmed on the steam bath till effervescence ceased. After cooling, the product was filtered and washed with hot thiosulphate solution until buff coloured. The final washings were with warm water. After drying, the acid was recrystallised from benzene. Melting point 161°C. Yield 70%.

Preparation/

Preparation of salicylic acid from o-iodo benzoic acid.

3 Grams of the iodo acid were dissolved in excess of bench sodium hydroxide solution, and boiled for one hour under reflux in the presence of 0.2 grams of copper bronze catalyst. On filtration and acidification, needle crystals separated which, on recrystallisation from boiling water, melted at 155°-156°C. A mixed melting point with salicylic acid gave 155°C. Yield 77%.

Preparation of o-methoxy benzoic acid.

3 Grams of o-iodo benzoic acid were added to the solution obtained by dissolving 0.6 grams of sodium in 20 c.c. of methyl alcohol. Copper bronze was added, and the mixture heated under reflux for four hours. The solution was then filtered, and some of the alcohol removed from the filtrate by warming on the steam bath. To the well cooled solution, concentrated hydrochloric acid was added, and the separated crystals filtered and recrystallised from boiling water. These when dry melted at 99°-100°C. and gave no halogen reaction with the sodium/

sodium test.

The weight obtained, 0.6 grams, represents a 33 1/3 % yield of methoxy acid.

Preparation of o-phenoxy benzoic acid.

Sodium (0.56 grams) was dissolved in excess of pure dry phenol. o-Iodo benzoic acid (3 grams) was added, together with some copper powder, and the product heated at 110°-112°C. for two hours. The mixture, when cool, was taken up with sodium hydroxide, and acidified. The crystals which separated, were extracted with ether in which they dissolved completely. The ether extract was shaken with sodium carbonate solution, and the alkaline extract acidified after filtration and warming to remove copper powder and a little dissolved ether respectively. The addition of hydrochloric acid to the cooled solution resulted in the deposition of a solid, which was twice recrystallised from aqueous alcohol. Melting point 112°-113°C.

(Beilstein/

(Beilstein quotes 113° C. for o-phenoxy benzoic acid).

Weight 0.78 grams. Yield 30%.

Preparation of 3-methyl-1-carboxydiphenyl ether.

o-Iodobenzoic acid (3 grams) was added to the solution obtained by dissolving 0.56 grams of sodium in 6 grams of m-cresol. Copper powder was added, and the product heated at 120° for two hours. The mixture when cool was poured into a separating funnel and extracted with ether. The ether extract was shaken with sodium carbonate solution, which in turn was filtered and warmed. On acidification of the alkaline extract, an oil separated, which speedily solidified. This was removed and dried. Two recrystallisations from ligroin gave a solid of melting point 95°-96°C. and weighing 1.1 grams. Yield 41% of theory.

(Beilstein quotes for this compound a melting point/

point of 95°C.).

Preparation of o-menthoxy-benzoic acid.

Sodium (0.6 grams) was dissolved in excess of l-menthol, and 3 grams of o-iodo-benzoic acid were added to the solution, together with 0.3 grams of copper bronze powder. The mixture was heated for two hours . After cooling, the product was shaken with ether, and sodium hydroxide, and the alkaline layer removed and acidified. The brownish product which separated was filtered, washed with water and dried. Two recrystallisations from ligroin gave a solid of melting point 177°-178°C. Weight 1 gram, representing a 33⅓ % yield.

Analysis: Required for o-menthoxy-benzoic acid,

C 73.9% H 8.7% .

Found 73.9% 8.8%.

Preparation/

Preparation of methyl o-iodo benzoate.

o-Iodo-benzoic acid (20 grams) was dissolved in 15 grams of thionyl chloride, and the solution refluxed for an hour, after which time no more fumes of hydrochloric acid were evolved. The excess thionyl chloride was removed under diminished pressure and the remaining acid chloride was treated with 25 c.c. of methyl alcohol. A vigorous reaction took place, and much hydrochloric acid gas was given off. The change was completed by warming for twenty minutes. Some of the methyl alcohol was then removed by distillation, and the remaining solution poured into water. The ester was extracted with ether, and the ether layer washed with dilute alkali till free from acidic products. The ether layer was dried over calcium chloride, and, after removal of the solvent, the ester was distilled. Boiling point 139°-141°/ 15 mm. Weight 16 grams. Yield 80%.

Preparation/

Preparation of methyl o-methoxy benzoate.

Methyl o-iodo-benzoate (3 grams) was added to a solution obtained by dissolving 0.43 grams of sodium in 15 c.c. of methyl alcohol. Copper bronze catalyst was added, and the product refluxed for three and a half hours. The alcoholic solution was then poured into 100 c.c. of sodium carbonate solution, and the ester extracted with ether. The ether layer was washed with dilute acid, and dried over calcium chloride. The ether was then removed, and the resulting ester distilled. Boiling point 129°-130°C./14 mm. It showed no iodide reaction in the sodium test. The weight of 2 grams represents a 62% yield. This is the most convenient method of obtaining this ester as, o-methoxy benzoic acid prepared from salicylic acid by methylation is very difficult to free from unchanged hydroxy acid.

Preparation of methyl o-menthoxy benxoate.

To a solution of 0.27 grams of sodium in excess l-menthol, 3 grams of methyl o-iodo-benxoate were added. A precipitation of sodium iodide started immediately after the addition of a trace of copper bronze. The product was heated for two hours/

hours and cooled. It was then taken up with ether and filtered. The ether and excess menthol were removed, and the ester fractionated. It boiled at 198°-200°C./13 mm. Yield 30%.

Analysis: Required. C 74.5%. H 8.97 %.
Found. C 74.5%. H 9.16 %.

It has been shown by Finkelstein (Ber., 1910, 43, 1528-1532) that organic chlorides and bromides may be converted into the corresponding iodides by boiling in acetone solution with sodium iodide. Finkelstein confined his researches to compounds containing side chain halogen, and found that the method did not work with acyl chlorides or compounds yielding unstable iodo-derivatives. The latter class includes substances containing several carboxyl or phenyl groups.

Unfortunately it was found that by boiling o-bromo benzoic acid in acetone solution, saturated with sodium iodide, in the presence of copper bronze, no apparent reaction had taken place after boiling for/

for 16 hours.

Two variations of this method suggested themselves. In the first place, in all the reactions studied during the present investigation the sodium salt of the bromo or iodo acid was used. Secondly, an increase in temperature might favour reaction. These two ideas were embodied in the following experiment.

Preparation of o-iodo-benzoic acid from o-bromo-benzoic acid.

Sodium (0. 12 grams) was dissolved in excess of ethyl alcohol, and 1 gram of o-bromo-benzoic acid added. The product was refluxed for 12 hours in the presence of copper bronze catalyst. A white precipitate was then found to have formed. The mixture was filtered and the filtrate acidified with concentrated hydrochloric acid. On well cooling the product, needle shaped crystals formed. After standing three hours in ice, the product was filtered, washed, dried, and recrystallised from ligroin. The crystals then melted at 158°-159°. A mixed melting point with o-iodo-benzoic acid gave no depression, while the product mixed with o-bromo-benzoic acid melted/

melted over a wide range starting at 135°C. The compound formed was therefore o-iodo-benzoic acid. Yield about 75%.

Preparation of o-nitro benzoic acid from o-iodo benzoic acid.

o-Iodo-benzoic acid (1 gram) was dissolved in a solution of 0.09 gram of sodium in 25 c.c. of propyl alcohol. Copper bronze was added and the product refluxed for twelve hours over 4 grams of silver nitrite, after which time it was filtered. The filtrate was acidified and thoroughly cooled. The crystals were filtered. The residue in the filter paper was extracted with dilute sodium hydroxide and filtered. On acidification, the product was added to the above crop. The crystals were then washed. They were recrystallised once from water, and once from ligroin and then melted at 141°C. A mixed melting point with iodo-acid gave a range beginning at 120°C. The compound moreover/

moreover contained nitrogen but no iodine, as revealed by sodium test. It was in fact o-nitro benzoic acid.

The weight 0.27 gram, represents a yield of 54%.

III. /

III. THE REACTIVITY OF THE BROMINE ATOM IN 8-BROMO-1-NAPHTHOIC ACID AND SOME USES OF THIS COMPOUND IN THE PREPARATION OF CERTAIN TYPES OF PERI-DERIVATIVES.

(a) Introduction.

The experimental work which follows is important not only from the theoretical, but also from the practical point of view. The bulk of the compounds described are probably not easily accessible from any other starting point than the one indicated, while the methods hitherto used for the preparation of the other derivatives, are inconvenient and laborious.

The preparation of naphtholactone has formerly been carried out in one of two ways.

(1) Jaubert (Gazz. **25**, 1, 247) has shown that by heating naphthalic acid in a current of dry air at 250°, the anhydride passes over in the form of yellow plates or needles. By a careful regulation of the temperature, the product is kept free from naphthalene.

When naphthalic anhydride is treated with concentrated ammonia (Behr. Dorp. A. 172, 266) naphthalimide is obtained as a reddish compound, which by

the method of Pisovschi(Bl. 1911,(4), 9, 87) is readily converted into 8-amino-1-naphthoic acid by treatment with the calculated amount of sodium hypochlorite.

By diazotisation and decomposition of the diazo-salt at room temperature, 8-hydroxy-1-naphthoic acid is obtained, which readily passes into the more stable naphtholactone.

(2) /

(2) α-Naphthoic acid is used as the starting material in the second method for the preparation of naphtholactone.

The nitration of this acid in the 5- and 8-positions has already been discussed in this thesis, while the method of isolation of the 8-nitro-1-naphthoic acid has been described. This compound readily undergoes reduction with ferrous sulphate. The yield of reduced product is, however, not very good.

The amino acid when diazotised and decomposed as indicated above, yields naphtholactone.

A compound normally prepared from naphtholactone is the 8-methoxy-1-naphthoic acid. By methylation of naphtholactone, Rule, Spence and Bretcher (J.C.S., 1928, 1500) have been able to obtain 8-methoxy-1-naphthoic acid. The method, however, is tedious, and gives only a poor yield of methoxy acid.

When salicylic acid is methylated using dimethyl sulphate, the reaction is by no means complete, and great difficulty is experienced in separating unchanged salicylic acid from o-methoxy benzoic acid. As might be expected, a similar difficulty arises in the case of 8-hydroxy-1-naphthoic acid. The quantity of this acid which remains unchanged after treatment with dimethyl sulphate, has to be separated from the 8-methoxy-1-naphthoic acid by conversion into an insoluble dyestuff.

The preparation of naphtholactone is easily carried out as described in the following pages, by merely boiling the 8-bromo-1-naphthoic acid with sodium hydroxide in the presence of copper powder.

The/

The methoxy acid can be obtained in fairly good yield, and very simply, by boiling a methyl alcoholic solution of sodium methoxide with the requisite amount of the sodium salt of the bromo acid. In fact this appears to be a general method for the preparation of both aliphatic and aromatic peri-ethers of α-naphthoic acid.

(b) Experimental.

The preparation of certain peri-alkyl ethers of α-naphthoic acid.

(1) Preparation of 8-methoxy-1-naphthoic acid.

Sodium (0.2 grams) was dissolved in 15 c.c. of methyl alcohol. To the methoxide solution was added 1 gram of 8-bromo-1-naphthoic acid and 0.2 grams of copper bronze. The mixture was refluxed for 4 hours, and allowed to stand overnight. Small white crystals were then found to have separated. On the addition of water, these dissolved, and the resulting solution was filtered and evaporated down. Concentrated hydrochloric acid was then added and the mixture well cooled. The product was filtered, washed and dried. The crystals were recrystallised twice/

twice from benzene, from which solvent they separated out as lustrous needles which lost their lustre on standing. These, when dry, melted at 159°-160°C. A mixed melting point with a sample of 8-methoxy acid gave no depression.

Weight 0.55 grams.

Yield - 69%.

(2) Preparation of 8-ethoxy-1-naphthoic acid.

8-Bromo-1-naphthoic acid (1 gram) was added to a solution of 0.2 grams of sodium in 15 c.c. of ethyl alcohol in a round-bottomed flask fitted with a ground-in air condenser. To the resultant solution was then added 0.2 grams of copper bronze powder. After boiling for two hours a precipitate appeared, and the boiling was continued for another two hours. Water was then added, and the product filtered. The filtrate was warmed on the steam bath to remove some alcohol, and then acidified with hydrochloric acid. After standing in the refrigerator for two hours, the product was filtered, and/

and washed with water. After drying, the residue was recrystallised twice from benzene, from which solvent it separated in needles resembling the 8-methoxy-1-naphthoic acid, and melting at 210°-211°C.

Calculated for 8-ethoxy-1-naphthoic acid,

C 72.2% H 5.55%

Found: C 72.14% H 5.61%

(3) Preparation of 8-propoxy-1-naphthoic acid.

Sodium (0.18 grams) was dissolved in excess of propyl alcohol. To the solution was added 8-bromo-1-naphthoic acid (1 gram) and 0.2 grams of copper bronze. The product, after boiling for one hour, deposited sodium bromide, the amount of which did not increase on boiling for another hour. The product was diluted with water, filtered, and acidified. The crystals were filtered, washed with water, and recrystallised from benzene. Melting point, 176°-177°C. (Mixed melting point with bromo acid melted at/

at 130-145°C.).

Weight 0.45 grams. Yield 50%.

Calculated for 8-propoxy-1-naphthoic acid

C 73%. H 6.1%

Found: C 72.8%.H 6.2%

(4) Preparation of 8-butyloxy-1-naphthoic acid.

0.5 Grams of 8-bromo-1-naphthoic acid was added to the solution of 0.09 grams of sodium dissolved in excess of butyl alcohol containing in suspension 0.2 gram of copper bronze catalyst. The product after boiling for five minutes had deposited sodium bromide. The heating was continued for two hours, and the product then poured into water. The excess alcohol was extracted with ether and the aqueous extract, after filtering and warming, was acidified. The crystals were filtered, washed, and dried. One recrystallisation from benzene gave a product of melting point 154°-155°C.

Weight 0.23 gram. Yield 50%.

Calculated for 8-butyloxy-1-naphthoic acid

C 73.8% H 6.5%

Found: C 73.7% H 6.7%

Two facts emerge from the above experiments, viz: (a) The greater ease with which the reaction proceeds as the series is ascended, due in all probability to the successive rises in temperature with increase in the molecular weights of the alcohols; and (b) The peculiar variations in the melting points of these alkyl ethers - a peculiarity which is also evidenced in the o-alkyl ethers of benzoic acid. This will be considered later.

The action of sodium hydroxide on 8-bromo-1-naphthoic acid.

8-Bromo-1-naphthoic acid (0.5 gram) was dissolved in excess of bench sodium hydroxide solution, and the product boiled in the presence of copper bronze for 30 minutes. The product was filtered, acidified with hydrochloric acid, and warmed in the steam bath for one and a half hours (to/

(to ensure complete conversion to naphtholactone). The product was filtered and dried, then recrystallised from ligroin. Yellow needles, weighing 0.16 gram, and therefore representing a 47% yield, were formed. M.p. 106°-108°C.

At this stage it may be mentioned that an attempt was made to prepare the acetyl derivative of 8-hydroxy-1-naphthoic acid. It was thought that the compound might possess, on account of its structural resemblance to acetyl salicylic acid, some physiological interest. Unfortunately, using acetyl chloride in pyridine solution and working up the product in the usual way, only naphtholactone (melting point 108°C.) was obtained from the hydroxy acid. It appeared, therefore, that the acetyl chloride had merely removed water from the 8-hydroxy-1-naphthoic acid.

Preparation/

Preparation of 8-menthoxy-1-naphthoic acid.

Sodium (0.2 gram) was dissolved in excess l-menthol and 1 gram of 8-bromo-1-naphthoid acid was added. The mixture was heated for sixteen hours at 110°-120°C. in the presence of copper bronze (0.2 gram). A great deal of darkening took place during the reaction, and this probably affected the yield adversely. The mixture was cooled and taken up with ether. On extraction with water, and acidification, a dark coloured product resulted, which was filtered off, and dried. Two recrystallisations from ligroin gave almost colourless crystals which were filtered and dried, giving prisms melting at 206°-207°C.
Weight 0.4 gram. Yield 30%.

Calculated for 8-(ℓ)-menthoxy-1-naphthoic acid

C 77.53% H 7.98%

Found: C 77.3% H 7.84%

Preparation/

Preparation of 8-phenoxy-1-naphthoic acid.

8-Bromo-1-naphthoic acid (1 gram) was added to a solution of 0.18 gram of sodium in excess of phenol, and 0.2 gram of copper bronze was added. The mixture was heated at 120°C. for four hours, and the dark coloured product was then cooled by pouring into water. It was extracted with ether to remove phenol. The aqueous solution was boiled, filtered and cooled. The solution was then acidified with hydrochloric acid, and the oil which separated, stirred. This soon solidified, and was filtered and dried. Two recrystallisations from a mixture of equal volumes of ligroin, and (88°-100°C.) petrol ether, gave short lustrous needles.

Melting point 139°-140°C.

Weight 0.4 gram. Yield 38%.

Calculated for 8-phenoxy-1-naphthoic acid

C 77.3% H 4.5%

Found: C 77.1% H 4.6%

Preparation/

Preparation of 8-benxyloxy-1-naphthoic acid.

1 Gram of 8-bromo-1-naphthoic acid was dissolved in excess benzoyl alcohol in which had previously been dissolved 0.2 gram of sodium. 0.2 Gram of copper bronze was added, and the mixture refluxed for two hours. After cooling, the product was transferred to a separating funnel and shaken up with ether. On extracting with water and working up in the usual way a brown solid was obtained which was filtered, washed and dried. Two recrystallisations from ligroin gave a melting point of 125°-126°C Yield 40%.

Calculated for 8-benzoyloxy-1-naphthoic acid

C 77.7% H 5.0%

Found: C 77.5% H 5.1%

Having/

Having studied the preparations of certain peri-ethers of α-naphthoic acid, attempts were made to prepare certain compounds containing carbon to carbon linkages.

In this connection it has been shown (Ullmann and A. Meyer. A. 332, 70) that when the methyl ester of o-iodo-benzoic acid is heated with copper powder, a temperature of 250°-260° is required for reaction to take place. The resulting compound is the dimethyl ester of diphenic acid.

Melting point 73°-74°C.

Moreover the dimethyl ester of 8:8-dinaphthyl 1:1'-dicarboxylic acid has been prepared in the department (W. Purcell. Unpublished Research) by heating the methyl ester of 8-bromo-1-naphthoic acid with copper at 180°C. The product (which could be recrystallised from ether) melted at 140°-141°C.

Now Lesslie and Turner (J.C.S. 1931, 1188) have described the preparation of 2-α-naphthyl-3:5-dinitro-benzoic ester from α-iodo-naphthalene, and ethyl 3.5-dinitro-2-benzoate, by heating the mixture in the presence of copper at 180°C.

The authors claim that this reaction went quantitatively in the above direction, and that, unexpectedly enough, no diethyl ester of 3:5:3':5'-tetra nitro diphenic acid was formed. It appeared, therefore, that by heating methyl o-iodo-benzoate with methyl-8-bromo-1-naphthoate (which appeared to be comparable in reactivity with one another) three compounds might result.

(a) The dimethyl ester of diphenic acid.
(b) The dimethyl ester of 8:8'-dinaphthyl 1:1'-dicarboxylic acid.
(c) The dimethyl ester of 8-(o-carboxy phenyl)-1-naphthoic acid.

By/

By keeping the temperature well below 250°C. the possibility of (a) being formed was practically eliminated.

The reaction between methyl o-iodo-benzoate and methyl 8-bromo-1-naphthoate in the presence of copper powder at 190°-200°C.

2.5 Grams of methyl 8-bromo-1-naphthoate were added to the same amount of methyl o-iodo benzoate in a small flask. Arrangements were made for efficiently stirring the mixture. The product was heated in an oil bath at 190°-200°C. and 4 grams of copper bronze were added over a period of 15 minutes. The stirring and heating were continued for three hours. The creamy mixture was extracted repeatedly with boiling ether, and the extracts cooled. The crystals which separated were filtered off, and melted at 124°-127°C. Two recrystallisations from methyl alcohol gave a product melting at 130°-131°C. This figure could not be raised although the compound always sintered a few degrees below the melting point. It was obvious that the crystals were not those of the dimethyl ester of diphenic acid. A

mixture/

mixture of the dimethyl ester of 8:8'-dinaphthyl 1:1'-dicarboxylic acid (melting point 148°C.) melted over a range beginning at 110°C. The only remaining possibility was methyl 8-(o-carbomethoxy phenyl)-1-naphthoate. The crystals weighed 1.43 grams, representing a 47% yield of this compound. They separate readily from methyl alcohol and ether, in the form of stout, almost colourless,needles.

Required for methyl 8-(o-carbomethoxy-phenyl)-1-naphthoate C 75.2% H 5.14%

Found: C 75.0% H 5.0%

Hydrolysis of methyl 8-(o-carbomethoxy-phenyl)-1-naphthoate.

0.13 Gram of the ester was heated for sixteen hours with 5 c.c. of concentrated ethyl alcoholic potassium hydroxide. The product was poured into 10 c.c. of water and the excess alcohol removed by warming. Hydrochloric acid was added, and a precipitate/

precipitate (largely of potassium chloride) was formed. The addition of a little water dissolved this, and the remaining insoluble acid was filtered, washed, and dried. The acid separates in the form of plates from rectified spirit.
Weight 0.09 gram. Melting point 231°-232°C.
The crystals are slowly soluble in cold sodium bicarbonate solution.

Analysis. Calculated C 74.0% H 4.1%
Found C 74.0% H 4.3%

The sodium salt of 8-bromo-1-naphthoic acid does not appear to react with the sodium derivative of diethyl malonate and acetoacetic ester, whether the reactions be attempted in the usual manner in alcoholic solution, or in the absence of extraneous solvent other than excess of the esters.

When the reaction is carried out in alcoholic solution/

solution, the only product which can be isolated is 8-ethoxy-1-naphthoic acid, and this only in poor yield. In the absence of alcohol, the diethyl malonate or acetoacetic ester darkens strongly, and even after prolonged heating only 8-bromo-1-naphthoic acid is recovered in an impure state.

Attempted preparations of 8-iodo-1-naphthoic acid from 8-bromo-1-naphthoic acid.

(a) The sodium salt of the bromo acid was boiled in propyl alcoholic solution with sodium iodide, in the presence of copper bronze catalyst. After heating overnight, a precipitate of sodium bromide had appeared. On filtering and adding concentrated hydrochloric acid, a precipitate appeared which was filtered off, dried, and recrystallised from benzene. The crystals so obtained melted over a range beginning at 140°C, and ending at 148°C. The product contained iodine. Recrystallisations from various solvents had no effect on the melting point. By analogy it was expected that the iodo-acid would melt above 178°C. and the melting point tube was therefore/

therefore immersed when the bath reached 170°C. The acid immediately melted however.

(b) A second method involving more prolonged heating resulted in the production of α-naphthoic acid.

From these experiments it would appear that the iodo acid was actually formed but that it decomposed, presumably at the temperatures used. Unfortunately, using ethyl alcohol as solvent, no formation of sodium bromide took place, even after boiling for 48 hours.

Attempted preparation of 8-nitro-1-naphthoic acid from 8-bromo-1-naphthoic acid.

Boiling the sodium salt of the bromo acid in alcoholic solution with silver nitrate led to no formation of 8-nitro-1-naphthoic acid, and the 8-bromo-1-naphthoic acid was recovered unchanged.

8-Bromo-5-nitro-1-naphthoic acid has been isolated in this department. W. Purcell (unpublished research) has obtained this compound by the nitration/

nitration of 8-bromo-1-naphthoic acid, and has actually shown the position of the nitro group to be in the 5- positions.

Preparation of 8-ethoxy-5-nitro-1-naphthoic acid.

8-Bromo-5-nitro-1-naphthoic acid (1 gram) was dissolved in a solution of 0.16 gram of sodium in 25 c.c. of ethyl alcohol. After the addition of 0.2 gram of copper bronze the mixture was boiled. After about twenty minutes the deposition of sodium bromide was observed and this appeared to be completed within an hour. The product was filtered and the filtrate acidified. On working up in the usual way, a yellow brown acidic product was obtained. This was recrystallised from alcohol (rectified spirit) from which solvent it separated out as needles of melting point of 214°-215°C. The yield of 8-ethoxy-5-nitro-1-naphthoic acid was 48%.

Calculated for 8-ethoxy-5-nitro-1-naphthoic acid

C 59.7% H 4.2%

Found: C 59.8% H 4.2%

V. CONCLUSIONS.

It may be taken that the lability or stability of a group or atom attached to a di-substituted aromatic nucleus is due to

(a) An effect transmitted through the bonds, depending in its nature on the second group, or to

(b) An effect transmitted through space from one group or atom to the other, and depending in its intensity on the nature and relative positions of the two substituents.

A third possibility is

(c) a combination of both the above effects.

It is generally assumed that the space effect is a powerful one which falls off very rapidly with increasing distance between the two groups, but that the bond influence may be transmitted with loss of intensity through the pair of conjugated bonds from the para-position. Unless the reactivity is masked by/

by steric hindrance, as undoubtedly occurs in many types of chemical change, it follows that an atom in position 1- may be activated to a greater extent by a suitable group in position 2- than when it occupies position 4-, not only because of the somewhat greater bond influence but on account of the greatly increased spatial effect. It can also be deduced that compounds in which these substituents are closer than in the ortho-position may possess the properties of ortho- compounds in an enhanced degree. The "bond" distance is, of course, at a minimum in ortho- derivatives, but the"space" distance between groupings in certain cases can be made considerably smaller than that existing in this type of compound.

The close spatial proximity of the groupings in the peri-positions has been demonstrated in the field of optical activity. The introduction of a $-CH_3$, -Cl, or $-OCH_3$ grouping into any position adjacent to a carboxylic complex containing an optically active carbon atom, lowers the optical rotatory power of the compound. Thus Rule, Hay and Numbers (J.C.S. 1926, 2118) observed in the

case/

case of d-β-octyl methoxy-benzoates, a progressive diminution in rotatory power on going from the para-compound to the ortho- compound.

The figures for the homogeneous esters at 20°C are:

	o-	m-	p-
M	+33.27	+ 93.73	+113.3

The optical rotatory powers of l-menthyl benzoate and of l-menthyl o-methoxy benzoate, in benzene solution, have been observed by A. Dunbar (unpublished research) and are found to have the following values:

	M_{5461} (In benzene) C = 5
l-menthyl benzoate	-280°
l-menthyl o-methoxy benzoate	+212°
Difference	68

Moreover the corresponding figures for l-menthyl 8-methoxy-1-naphthoate and for l-menthyl naphthoate have been obtained by Bretscher, Rule and Spence (J.C.S. 1929, 2516) and were found to have the following values:

1/

	M_{5461} (in benzene) C = 5
l-menthyl naphthoate	-319°
l-menthyl 8-methoxy-1-naphthoate	-157
Difference	162

The characteristic influence of the methoxy group is therefore very much greater in the peri- than in the ortho- compound, and is readily explained on the assumption that peri- groups are in closer proximity than those in the ortho- position.

The proximity of the groupings in peri-substituted carboxylic acids is undoubtedly responsible for the difficulty experienced in esterifying such compounds. In this connection mention may be made of the work of Eckstrand (J. Pr. 1888, 2, 38, 150) who found that no perceptible esterification took place on passing hydrochloric acid gas into an ethyl alcoholic solution of 8-chloro-1-naphthoic acid. A similar observation has been made with 8-bromo-1-naphthoic acid, during the course of the present work. Rule, Spence and Bretscher (J.C.S. 1929, 2516) experienced similar difficulties with 8-nitro-1-naphthoic acid.

Moreover/

Moreover such acids, resistant as they are to esterification, once esterified, give rise to esters which are very resistant to hydrolysis - treatment with fused potassium hydroxide often being required.

The observations of Mills and Elliot (J.C.S. 1928, 1291) have demonstrated in a very effective way the closeness of groupings in peri- positions to one another. They found that N-benzene-sulphonyl-8-nitro-1-naphthyl-glycine could be resolved into active forms - a resolution depending, apparently, on the inability for free rotation of the peri-groups, owing to their close proximity to one another. No such resolution has yet been found possible among ortho- derivatives. The above observations, mainly of a physical nature in the field of optical activity, are in keeping with the chemical relationships which exist between ortho- and peri- derivatives.

The tendencies which exist in many ortho-compounds to form anhydrides, are accentuated in the corresponding peri- derivatives. Thus 8-hydroxy-1-naphthoic acid, and 8-amino-1-naphthoic acid, are relatively unstable, and tend to pass into ring compounds, viz.

Similarly naphthalic acid (analogous to phthalic acid) sublimes without melting, yielding naphthalic anhydride by the elimination of water.

From what has been said, it would therefore appear that the effects observable in ortho-compounds are intensified in the corresponding peri-derivatives. The experimental work in this thesis goes largely to confirm that conclusion, and to show, moreover, that the reactivity of the groupings and atoms concerned, are due, in the main, to effects transmitted through space from secondary substituents. From the work on 8-nitro-1-naphthoic acid, it follows that its ready conversion to 8-chloro- or 8-bromo-1-naphthoic acids by means of thionyl chloride, is due to the spatial relationships existing between the nitro- and carboxyl groupings in this acid. The proximity of the carboxyl group in fact gives rise to a reactivity of the nitro- group which cannot be due to a bond transmission. If the reactivity

were/

were due to an activating effect transmitted through the bonds from the carboxyl group, it follows that o-nitro-benzoic acid should easily be converted into o-chloro-benzoic acid by treatment with thionyl chloride. Actually o-nitro-benzoic acid reacts quite normally with this reagent yielding o-nitro benzoyl chloride - which however is a somewhat unstable compound in contradistinction to its meta- and para-isomers. Similarly 5-nitro-1-naphthoic acid, when treated with thionyl chloride, yields no 5-chloro-1-naphthoic acid. A point which must be stressed in this connection is the remarkable ease with which the reaction occurs in the case of 8-nitro-1-naphthoic acid. In the experience of former investigators vigorous conditions were usually required to replace nitro-groups by chlorine atoms by means of thionyl chloride.

The instability of the nitro- group in 8-nitro-1-naphthoic acid is still further borne out by the formation of the compound dichloro-naphtho-styril. Thionyl chloride is quite a well known chlorinating agent, but we have been unable to trace in the literature any former mention of its reducing properties towards nitro- compounds. It was found, in this connection, that sulphuryl chloride/

chloride, although capable of converting 8-nitro-1-naphthoic acid in part to 8-chloro-1-naphthoic acid, does not produce any formation of dichloro naphthostyril. This difference may be assumed to depend on the fact that sulphuryl chloride does not possess the properties of a reducing agent.

Let us now turn to the work which has been done on the replacement of the halogen atoms in ortho-iodo-benzoic acid, and 8-bromo-1-naphthoic acid, under the influence of copper bronze catalyst. The action of the catalyst it may be said at the outset is inexplicable, but in its absence the reactions did not proceed, at all events under the mild experimental conditions employed.

The question of using other catalysts such as finely divided nickel or silica gel has not been investigated in the present work. It was found that o-chloro-benzoic acid had none of the reactivity of o-bromo-benzoic acid towards the reagents used by Hurtley (loc. cit.) such as caustic soda, and sodium alkoxides. Moreover, o-iodo-benzoic acid was even more reactive than the bromo-acid as proved by the/

the speed with which it reacted with sodium alkoxides. The iodo-acid also reacted with silver nitrite to form o-nitro-benzoic acid. In these respects the extraordinary reactivity of o-iodo-benzoic acid (in the presence of the catalyst) is almost comparable with that of the alkyl halides. One of the most interesting changes carried out with the o-bromo-acid is its conversion into o-iodo-benzoic acid. As has already been mentioned, the conversion of bromides into iodides by boiling with solutions of sodium iodide has only previously been observed in the case of aliphatic compounds or aromatic derivatives containing the halogen in an aliphatic side chain.

Among the halogenated naphthoic acids it was found that 8-bromo-1-naphthoic acid possessed a similar reactivity towards sodium alkoxides and phenoxides, although the bromine atom could not be replaced by the nitro group or iodine. Sodio-malonic ester and sodio-acetoacetic ester were also non-reactive towards the bromo acid, possibly owing to the steric hindrance offered to the entrance of such large groups. 8-Chloro-1-naphthoic acid

failed/

failed to show any reactivity at all under the same conditions, even with alkoxides.

The melting points of the peri-ethers of α-naphthoic acid show a peculiar variation with rising molecular weight, as illustrated in graph A following. As is shown in graph B, the melting points of the o-ethers of benzoic acid also show fluctuations, which differ however from those of the corresponding peri- derivatives.

From the work which has been done with compounds containing reactive halogens, it may be concluded that o-iodo-benzoic acid possesses a reactivity camparable with, but somewhat greater than that of 8-bromo-1-naphthoic acid, and that the latter contains a bromine atom more reactive than the bromine atom in o-bromo-benzoic acid. These effects can only be explained by assuming that the reactivities are largely governed by the effect of the carboxyl group on the halogen atoms concerned.

These effects are probably responsible for the fact that we have been unable to prepare 8-iodo-1-naphthoic acid. It is possible that the size of the iodine atom prevents it from entering the 8-position if the 1-position is already occupied by

a/

a carboxyl group. This was indeed thought to be the explanation when we found that in some of the attempts to prepare this acid by the mercuration method, only α-naphthoic acid was obtained. It would appear that on the decomposition of the mercuration product, the 8-position is left momentarily vacant and competition exists between an iodine and a hydrogen atom to occupy this position. By reason of its smaller size the hydrogen atom effects an entrance. α-Naphthoic acid was also obtained on one occasion when boiling sodium 8-bromo-1-naphthoate with sodium iodide in propyl alcoholic solution.

It will be remembered that o-bromo-nitrobenzene was found not to be reactive under similar conditions towards the sodium alcoholate in the presence of copper bronze. This is even more remarkable when we remember the figures quoted by Wood and Davis (see p. 44) for the relative activating effects of nitro- and carboxyl groups. And in the naphthalene series an examination of the reactivity of the bromine atom in various nitro-bromo-naphthalenes has recently led Salkind (Ber., 1931, 64, 1218) to/

to conclude that the activating influence of the nitro group only extends to substituents in the same ring. It is obvious then that although the mode of action of the catalyst is unknown, its activating effect is connected preferentially with the carboxyl group.

In the case of the formation of 8-ethoxy-5-nitro-1-naphthoic acid from sodium 8-bromo-5-nitro-1-naphthoate and sodium ethoxide, it was observed that the reaction proceeded much more quickly than when we used sodium 8-bromo-1-naphthoate and sodium ethoxide. This result was expected and is probably due to a second activation of the bromine atom by the nitro- group - an activation, be it noted, unconnected with the presence of the catalyst.

The preparation of 8-(o-carbomethoxy-phenyl)-methyl-1-naphthoate is really an ordinary Ullmann reaction. The main points of interest about the preparation are: (a) the fact that none of the possible alternative compounds appear to be formed and (b) the relative insolubility of the ester, which enables it to be readily recrystallised from ether or methyl alcohol.

V. /

V. SUMMARY.

(1). The action of thionyl chloride on 8-nitro-1-naphthoic acid resulting in the replacement of the nitro- group by a chlorine atom has been studied, and the reaction considered in the light of its application as a possible method for the preparation of 8-chloro-1-naphthoic acid. The investigation has been extended to the corresponding reaction with thionyl bromide. The action of thionyl fluoride has not been considered owing to the difficulty of dealing with this reagent, while thionyl iodide has so far resisted all attempts at preparation.

(2). The various other possible means of preparation of the 8-chloro- and 8-bromo-1-naphthoic acids have been studied and developed. The most efficient method for their preparation has been found to be that indicated by Leuck, Perkins and Whitmore (J.A.C.S., 1929, 51, 3363) by the mercuration of naphthalic acid and subsequent treatment/

treatment with bromine.

(3). Attempts to prepare 8-iodo-1-naphthoic acid have been unsuccessful and there is a possibility that this compound cannot exist at moderate temperatures.

(4). The reactivities of the bromine atom in 8-bromo-1-naphthoic acid, and the iodine atom in o-iodo-benzoic acid, under the influence of copper bronze catalyst, have been investigated. The activity of these atoms has been made the basis of preparative methods for compounds of different types.

(5). The experimental work has brought out points of resemblance and difference between the ortho-compounds in the benzene series, and peri- compounds in the naphthalene series. The results tend to show that the latter derivatives possess the properties of the former in an enhanced degree, due, presumably, to the greater spatial proximity of groupings in the peri- series.

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